Diabetic Complications Consortium FINAL REPORT

Application Title: Glucose regulation of hypertriglyceridemia

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1. Project Accomplishments:

We have studied the effects of streptozotocin-induced diabetes and glucose reduction on hepatic production of triglyceride. The uncertain issue is the importance of gene regulation versus substrate delivery in liver production of triglyceride in the setting of diabetes. We have shown the following:

1. Insulin deficient diabetes does not modulate gene regulating de novo liver fatty acid synthesis.
2. Although plasma triglyceride is increased with diabetes, this is not associated with increased liver triglyceride secretions.
3. Streptozotocin-induced diabetes leads to a marked reduction in liver lipoprotein lipase activity in peripheral tissues.
4. Use of models in which insulin resistance was created by placing mice on a high fat diet did not alter regression of atherosclerosis.

2. Specific Aims:

Aim 1 iwas to determine why glucose reduction reduces triglyceride levels in diabetic mice.
Aim 2 studied the effects of acute hypertriglyceridemia and insulin-deficient diabetes on HDL composition and function.

Aim 1. We have complete Aim 1 and published these results. We have studied control mice and mice with modulation of lipoprotein lipase (both deletions and transgenic overexpression). Despite several studies using mice with defects in insulin receptors that have shown the essential role(s) of insulin signaling in de novo triglyceride synthesis, we have found no similar effects in animals with insulin deficiency, but sufficient amounts of insulin to maintain life. Liver secretion of triglyceride was not altered and we found no reduction in FASN or SCD1, genes within the pathway of de novo synthesis Our data support the hypothesis that in vivo the major regulator of triglyceride production in diabetes is substrate and not changes in gene expression that are created in the extreme using genetic modified mice.

Factors affecting plasma triglyceride removal from plasma were altered in diabetic mice. Postprandial lipemia was markedly increased with diabetes. This was associated with reduced lipoprotein lipase mRNA levels and activity in skeletal muscles. This effect mimicked what is seen in humans. Diabetes leads to increased postprandial lipemia.

We also studied mice with altered lipoprotein lipase production. Mice with a heterozygous deletion of lipoprotein lipase had much more markedly hyperlipidemia than did wild type mice. In concert with this, mice with additional lipoprotein lipase due to transgenic expression in skeletal muscle were protected form diabetes-induced hypertriglyceridemia. Again these data likely reflect human physiology as some patients with diabetes develop marked hypertriglyceridemia; some of these patients have been found to have lipoprotein lipase molecular defects.

Aim 2. We also assessed effects of diabetes on circulating levels of HDL and HDL composition. In our model we found no significant effect of diabetes on HDL lipid or protein composition. Perhaps this reflected the relatively minor increased in triglyceride levels in our diabetic mice. Or diabetes mediated changes in HDL might require the presence of cholesteryl ester transfer protein. In contrast, lipoprotein lipase deficiency leads to a marked reduction in HDL levels; 50% within 6 hours. We suspect that the effects of diabetes on lipoprotein lipase need to be greater than those found due to diabetes alone; like many enzyme deficiencies 50% reduction alone is insufficient to affect whole body or cellular metabolism.

3. Publications:

Lipolysis, and not hepatic lipogenesis, is the primary modulator of triglyceride levels in streptozotocin-induced diabetic mice. Willecke F, Scerbo D, Nagareddy P, Obunike JC, Barrett TJ, Abdillahi ML, Trent CM, Huggins LA, Fisher EA, Drosatos K, **Goldberg IJ**. Athero Thomb Vasc Biol. 2015 35:102-10. PMID:25395613

Effects of high fat feeding and diabetes on atherosclerotic regression in LDL receptor knockout mice using low-density lipoprotein receptor gene therapy. Willecke F, Yuan C, Grauer L, Oka K, Chan L, Hu Y, Barnhart S, Bornfeldt KE, **Goldberg IJ,** Fisher EA. Plos 1. 2015 10:e0128996. PMID: 26046657